Understanding Angiogenesis in the Eye

Physiological Control of Angiogenesis

Angiogenesis, also called neovascularization, occurs in the healthy body for healing wounds and for restoring blood flow to tissues after injury or insult. In females, angiogenesis also occurs during the monthly reproductive cycle (to generate the endometrium, to form the corpus luteum) and during pregnancy (to build the placenta).

Physiologically, the body controls angiogenesis through a series of "on" and "off" regulatory switches:

- The main "on" switches are known as angiogenesis growth factors (cytokines)
- The main "off switches" are known as endogenous angiogenesis inhibitors

When angiogenic growth factors are produced in excess of angiogenesis inhibitors, the balance is tipped in favor of blood vessel growth. When inhibitors are present in excess of stimulators, angiogenesis is stopped. The normal, healthy body maintains a perfect balance of angiogenesis modulators. In general, angiogenesis is "turned off" by with more inhibitors being produced than stimulators.

In the healthy eye, the regulation of angiogenesis is critical for preserving visual clarity. Normally avascular tissues include the cornea, and the aqueous and vitreous fluids. Neovascularization in the eye leads to vision loss and blindness in a number of significant conditions:

- **Pterygium**
  Pterygium is a proliferation of fibrovascular tissue on the surface of the eye, associated with ultraviolet light exposure. Within the pterygium are abundantly proliferating blood vessels that promote pannus growth and progression.

- **Corneal Neovascularization**
  Invasion of new blood vessels into the normally avascular cornea occurs after infection and injury. Corneal neovascularization may be induced by a number of angiogenic growth factors. Basic fibroblast growth factor (bFGF) is normally sequestered within Descemet's membrane and may be mobilized by injury. Inflammatory cells, such as macrophages and monocytes, also contain various angiogenic growth factors and corneal inflammation is a common stimulus for neovascularization.

- **Rubeosis Iridis**
  Neovascularization in the trabecular meshwork of the anterior chamber is observed in diabetes. New blood vessels obstruct aqueous outflow leading to glaucoma. Diffusible angiogenic factors, such as vascular endothelial growth factor (VEGF), are thought to originate from ischemic retinal tissues and promote neovascularization in the anterior chamber.

- **Retinal Neovascularization**
  Ischemia is thought to be the primary stimulus for neovascularization in the retina. Local hypoxia leads to upregulation of gene expression for hypoxia inducible factor-1 alpha (HIF-1alpha), which in turn, stimulates production of VEGF. While a number of angiogenic growth factors have been detected in vitreous fluid and retinal tissues, VEGF is regarded as the primary angiogenic factor responsible for retinal neovascularization. VEGF is also known as vascular permeability factor (VPF), and pathological retinal microvessels are leaky. VEGF also serves as a paracrine survival factor for angiogenic endothelial cells. Pericytes, associated with the retinal microvasculature, normally inhibit angiogenesis by secreting activated transforming growth factor-beta (TGF-beta). The loss of pericytes preceding diabetic retinopathy may promote neovascularization by decreasing levels of this endogenous angiogenesis inhibitor.

- **Choroidal Neovascularization**
  Angiogenesis originating from the choroidal circulation (subretinal neovascularization) is associated with macular edema and degeneration. The angiogenic growth factors, VEGF and FGF are also associated with this process.

- **Ocular Tumors**
  Both primary and metastatic tumors in the eye are dependent upon angiogenesis for growth and progression. Uveal melanomas have recently been reported to form microvessels in the absence of vascular endothelial cells, but this phenomenon remains controversial. For more information about tumor angiogenesis, please visit our Providers-Oncology site.

List of known angiogenic growth factors

Angiogenin
Angiopoietin-1
Del-1
Fibroblast growth factors: acidic (aFGF) and basic (bFGF)
Follistatin
Granulocyte colony-stimulating factor (G-CSF)
Hepatocyte growth factor (HGF) /scatter factor (SF)
Interleukin-8 (IL-8)
Leptin
Midkine
Placental growth factor (PlGF)
Platelet-derived endothelial cell growth factor (PD-ECGF)
Platelet-derived growth factor-BB (PDGF-BB)
Pleiotrophin (PTN)
Proliferin
Transforming growth factor-alpha (TGF-alpha)
Transforming growth factor-beta (TGF-beta)
Tumor necrosis factor-alpha (TNF-alpha)
Vascular endothelial growth factor (VEGF)/vascular permeability factor (VPF)

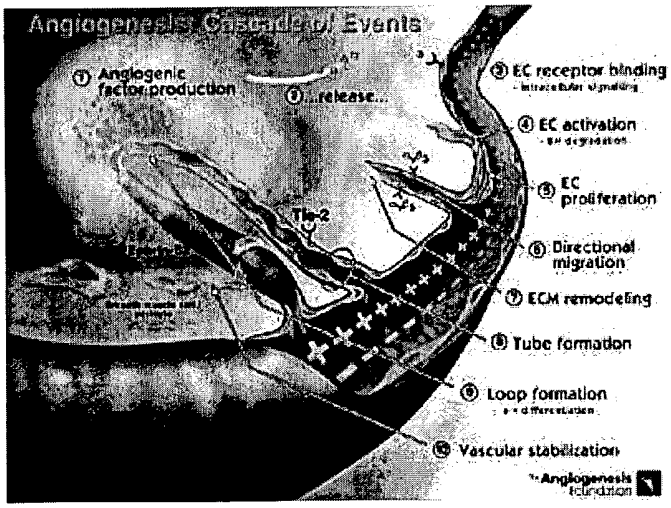
The Angiogenesis Process: How Do New Blood Vessels Grow?

The process of angiogenesis occurs as an orderly series of events:

1. Tumors produce and release angiogenic growth factors (proteins) that diffuse into the nearby tissues

2. The angiogenic growth factors bind to specific receptors located on the endothelial cells (EC) of nearby preexisting blood vessels

3. Once growth factors bind to their receptors, the endothelial cells



become activated. Signals are sent from the cell's surface to the nucleus. The endothelial cell's machinery begins to produce new molecules including enzymes

4. Enzymes dissolve tiny holes in the sheath-like covering (basement membrane) surrounding all existing blood vessels

5. The endothelial cells begin to divide (proliferate), and they migrate out through the dissolved holes of the existing vessel towards the diseased tissue (tumor)

6. Specialized molecules called adhesion molecules, or integrins (avb3, avb5) serve as grappling hooks to help pull the sprouting new blood vessel sprout forward

7. Additional enzymes (matrix metalloproteinases, or MMP) are produced to dissolve the tissue in front of the sprouting vessel tip in order to accommodate it. As the vessel extends, the tissue is remolded around the vessel

8. Sprouting endothelial cells roll up to form a blood vessel tube

9. Individual blood vessel tubes connect to form blood vessel loops that can circulate blood

10. Finally, newly formed blood vessel tubes are stabilized by specialized muscle cells (smooth muscle cells, pericytes) that provide structural support. Blood flow then begins

Endogenous Angiogenesis Inhibitors

Endogenous inhibitors of angiogenesis are also present in healthy and diseased tissues. These inhibitors are thought to be involved in maintaining the normally avascular state of ocular and other tissues:

Angiostatin (plasminogen fragment)
Antiangiogenic antithrombin III (aaATIII)
Canstatin
Cartilage-derived inhibitor (CDI)
CD59 complement fragment
Endostatin (collagen XVIII fragment)
Fibronectin fragment
Gro-beta
Heparinases
Heparin hexasaccharide fragment
Human chorionic gonadotropin (hCG)
Interferon alpha/beta/gamma
Interferon inducible protein (IP-10)
Interleukin-12 (IL-12)
Kringle 5 (plasminogen fragment)
Metalloproteinase inhibitors (TIMPs)
2-Methoxyestradiol (2-ME)
Pigment epithelial-derived factor (PEDF)
Placental ribonuclease inhibitor
Plasminogen activator inhibitor
Platelet factor-4 (PF4)
Prolactin 16kD fragment
Proliferin-related protein
Retinoids
Tetrahydrocortisol-S
Thrombospondin-1v Transforming growth factor-beta

Tumistatin
Vasculostatin
Vasostatin (calreticulin fragment)